National Institute of Allergy and Infectious Diseases / Division of Microbiology and Infectious Diseases	**Policy** DMID Assessment of Safety Signals	No: DMID.SFTY.001
	Approval Date: 4 May 2009 Effective Date: 6 May 2009	Version: 1.0

1.0 Purpose:

1.1 In support of the NIAID/DMID Policy and Guidelines for Data and Safety Monitoring, and NIAID Clinical Terms of Award, this policy defines the DMID processes for assessment of safety signals associated with research-related activities during the conduct of DMID-supported clinical research for which there is a medical monitor assigned for safety oversight.

2.0 Scope: This policy applies to,

2.1 Division of Microbiology and Infectious Diseases (DMID) staff responsible for the oversight of DMID-supported clinical research.

2.2 Principal Investigators and their staff conducting DMID-supported clinical research.

2.3 All DMID-supported clinical research, regardless of funding mechanism, consistent with the *NIH Policy for Data and Safety Monitoring* issued on June 10, 1998 (http://grants.nih.gov/grants/guide/notice-files/not98-084.html), and *Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials* issued on June 5, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html).

3.0 Background:

3.1 NIH policy requires data safety and monitoring for all NIH-funded clinical trials. http://www3.niaid.nih.gov/research/resources/toolkit/attachments/DSMB_Policyv2.pdf

3.2 Per NIH/NIAID/DMID Policy and Guidelines for Data and Safety Monitoring:

- The Division of Microbiology and Infectious Diseases (DMID) supports, through both the contract and grant mechanisms, a large number of clinical studies and trials. All DMID studies are conducted in accordance with DHHS regulations 45 CFR 46, which provide for the protection of study participants. To assure that procedures are in place to protect the safety of participants while assuring the validity and integrity of the study, DMID has adopted policies which mandate that a safety monitoring plan be established for all clinical trials. This requirement pertains to all studies that evaluate investigational test articles, studies in which there is a potential for harm to participants, and other studies in which independent assessments are required to assure objectivity.

- All DMID-sponsored Phase III trials are subject to Data Safety and Monitoring Board (DSMB) review. DSMB oversight should be considered for other clinical trials, such as masked (blinded) Phase I and II trials and for some unmasked Phase II trials.

- DMID Safety Monitoring Committee (SMC) is an independent group of experts that advises DMID and the study investigators for many Phase I and smaller Phase II trials.

- Safety Committees (DSMBs and SMCs, collectively) meet regularly, and whenever any special need arises to review study conduct and cumulative study data, to recommend whether the study should continue without change, be modified, or terminated.

- Safety Committees are advisory to DMID and their recommendations, while given careful considerations, are not binding.

4.0 Definitions:

Clinical Research – Per the NIAID definition, patient-oriented research, including epidemiologic and behavioral studies, outcomes research, and health services research; research on mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies, not including in-vitro studies using human tissues not linked to a living individual.

Clinical Site Monitors - Monitoring of a clinical trial by people outside of the research site. This independent group performs several functions, including but not limited to; Ensuring the rights, safety and well being of human subjects enrolled in clinical research studies; verifying the integrity of the data collected; ensuring site compliance with the protocol approved by the institutional review board (IRB)/international ethics committee (IEC), other documents, applicable regulatory requirements, ICH GCP guidelines, adequacy of staff and facilities.

Clinical Project Manager (CPM) – DMID primary point of contact responsible for the planning, coordination and management of DMID-supported clinical research throughout the life cycle of the protocol. Provides DMID recommendations to IND-holder.

Data Safety Monitoring Board (DSMB) –A DSMB is an independent group of experts that advises DMID and the study investigators. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to DMID concerning the continuation, modification, or termination of the trial. DSMBs meet regularly and whenever any special need arises to review study conduct and cumulative study data, and to recommend whether the study should continue without change, be modified, or be terminated.

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Halting / Stopping rule - Safety findings which may temporarily suspend enrollment and/or study interventions until a safety review is convened.

Independent Safety Monitor (ISM) - The ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring. An ISM could be the sole monitor for the study or may perform this role as a member of a Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC).

Medical Monitor - Provides input on safety considerations during development of protocol and associated documents, and safety oversight throughout the life cycle of the clinical research including evaluation, assessment and monitoring of safety events and protocol deviations; participates in safety oversight committees, and consults with Independent Safety Monitors (ISMs).

Safety Review – The outcome of the review is a decision as to whether the study (or intervention for an individual or study cohort) should continue per protocol, continue to be halted for additional investigation, be discontinued, or be modified before proceeding.

Study Team - All DMID members responsible for discussing the safety events / outcome(s) relative to safety events and potential suspension. Study team members are generally comprised of representatives from DMID/OCRA, Medical Monitor (MM), or Director of OCRA or designee if assigned MM is not available; DMID/ORA, if study is under IND; DMID Branch/Program representative(s); DMID personnel, including, but not limited to, the Project Officer for the clinical research site, pharmacist or consulting specialist (if available); and IND holder (non-DMID).

Safety Committee(s) – For this policy, this term refers collectively to the DSMB and SMC.

Safety Signal – A report, or report of an event with unknown causal relationship to clinical research (inclusive of clinical trials) or new information on a previously identified association. These events must be investigated further to validate/confirm an association. (Refer to *References,* section 7 of this policy)

Safety Monitoring Committee (SMC) - A SMC is a group comprised of independent experts that advise DMID and the study investigators on safety reports from Phase I and some Phase II trials. The primary responsibility of the SMC is to monitor participant safety.

Safety Oversight Coordinator (SOC)– Working with the Pharmacovigilance contractor, the DMID SOC oversees and coordinates the safety reporting system for global reporting of serious adverse events (SAEs) in global clinical trials (Phase 1, 2, 3 and 4) with investigational as well as licensed products. Oversees and coordinates the formulation and proper functioning of safety committees, DSMBs and SMCs.

Suspension – A DMID-supported clinical research activity (enrollment, intervention, operation) is halted.

5.0 Responsibilities:

5.1 DMID Medical Monitor (MM) is responsible for monitoring the safety of participants in DMID-supported clinical research

5.2 DMID personnel assigned responsibility for safety oversight are responsible for investigating, confirming/validating and communicating to investigational sites and appropriate authorities, the safety-related event(s) precipitating an action or consideration for suspension of a clinical research activity. If necessary, the Associate Director of Clinical Research is available to arbitrate disputes resulting from internal DMID review prior to review by the Safety Committee. DMID provides the final determination of action after consideration the Safety Committee's recommendation.

5.3 Principal Investigators/Clinical research sites conducting DMID-supported clinical research are expected to document and communicate safety-related events, as defined in the protocol, NIAID Clinical Terms of Award for the grant, applicable regulations, or applicable agreements, to their respective Institutional Review Boards (IRBs), and DMID in the required timeframe. The Principal Investigator is responsible for ensuring the appropriate documentation is available for DMID clinical site monitors and DMID personnel to review.

5.4 The Safety Committee is responsible for independently reviewing the clinical research and advising DMID on the appropriate course of action, whether to continue, modify or terminate the clinical research.

6.0 Implementation:

6.1 DMID confirms and reviews the safety information received, and determines the appropriate course of action.

6.1.1 Information is received from a number of sources, including clinical site investigators, clinical site monitors, a Data Coordinating Center (DCC), Independent Safety Monitor (ISM), corporate sponsor, manufacturer, safety committee report, pharmacovigilance, or other clinical research sources. For the purposes of this process, the clock starts when an involved DMID staff member becomes aware of the potential safety signal.

6.1.2 DMID Medical Monitor (MM), in consultation with appropriate study team members, reviews the potential safety report(s) against the following criteria.

6.1.2.1 A defined protocol stopping rule is met.
6.1.2.2 An event or cluster of events not described in the existing halting rules occurred and requires a DMID safety evaluation.
6.1.2.3 An event occurred which raises a safety/administrative concern, but no need for change in clinical research implementation.

6.1.3 Following the review of the safety report(s) an internal meeting convenes to review and investigate the safety information, request additional information as needed, and determines the appropriate and timely course of action to minimize risk and protect subject safety.

6.1.4 If appropriate, DMID report of an investigation is made available to the Safety Committee for review and recommendations.

6.2 DMID notifies appropriate parties of determinations regarding the clinical research safety report(s) under review

Note: Under the IND or IDE, the sponsor is required to provide the FDA with safety reports of serious adverse events. Under the NIAID Clinical Terms of Award, the awardee must submit copies to the responsible NIAID program officer, as directed in these terms, Part C, *Safety Reporting Requirements*.

6.2.1 **When there is no IND involved**:

6.2.1.1 DMID CPM promptly notifies the clinical sites, Independent Safety Monitor, appropriate DMID Branches/Offices, and DMID contractors of the clinical research activities that are suspended *pending* the safety committee review.

6.2.2 **When the IND is held by DMID:**

6.2.2.1 DMID CPM promptly notifies the clinical sites, Independent Safety Monitor, appropriate DMID Branches/Offices, and DMID contractors of the clinical research activities that are suspended *pending* the safety committee review.

6.2.2.2 DMID Branch/Office notifies the DMID Regulatory Affairs Specialist to ensure timely official communications to the U. S. Food and Drug Administration (FDA).

6.2.3 **When the IND is not held by DMID;**

6.2.3.1 DMID reviews and approves protocols and amendments. DMID provides the sponsor with recommendations, determinations or assessments for protocol or related safety events. For studies conducted under another sponsor's IND, that sponsor will report safety data to DMID.

6.3 Safety Committee meets to review the safety report(s) and available information

6.3.1 If a halting rule is met, the Safety Committee reviews available information and provides DMID with recommendations for the continued conduct of the clinical research.

6.3.2 If no halting rule is met, the study team determines the need to convene the Safety Committee.

6.4 **DMID reviews Safety Committee recommendations**

6.4.1 The DMID Medical Monitor, in consultation with the study team, determines if the Safety Committee's recommendations will be accepted, modified or rejected.

6.5 **DMID communicates final determination of the safety report(s) under review.**

6.5.1 **When the IND is held by DMID**;
The DMID CPM promptly notifies the clinical research sites, DMID staff, and DMID contractors, of the outcome of the Safety Committee / DMID review and determinations for continuation, modification or termination of DMID-supported clinical research activities.

When the Safety Committee recommends the temporary or permanent stopping of the study in order to protect human subjects, the DMID Office of Regulatory Affairs (ORA) representative will provide documentation of the Safety Committee / DMID determinations and a meeting summary to the FDA / regulatory authorities.

6.5.2 **When there is no IND involved;**
The DMID CPM promptly notifies the clinical research sites, DMID staff, and DMID contractors, of the outcome of the Safety Committee / DMID review and determinations for continuation, modification or termination of DMID-supported clinical research activities. Final decisions regarding ongoing safety reporting requirements for research not performed under an IND or IDE will be made jointly by NIAID and the awardee.

6.5.3 **When DMID supports the IND not held by DMID;**
The DMID CPM promptly communicates safety report review, recommendations to sponsors of non-DMID held INDs. When the DSMB recommends the clinical research is stopped and DMID agrees, *and the sponsor does not agree and decides to proceed with the study*, DMID will meet to decide if, how and when to continue funding. The Project Officer, the Office of the Director, ORA, OCRA, and other appropriate parties as needed, will be involved in the decision-making, and the process necessary to implement the decision.

6.6 **Additional reviews of serious, unexpected, and related adverse events** by the DMID / OCRA Medical Monitor, Safety Committee, IEC/IRB, corporate sponsor(s), or the FDA or relevant local regulatory authorities may also result in suspension of further research interventions/administration of study product at the clinical sites.

6.6.1 For FDA clinical hold of DMID-supported clinical research conducted under a DMID-held IND, refer to NIAID Clinical Terms of Award, Section C.
The awardee must notify NIAID if FDA places the study on clinical hold and provide NIAID any written comments from FDA, written responses

to the comments, and documentation in writing that the hold has been lifted.

7.0 References:

7.1 NIAID Clinical Terms of Award
7.2 NIH/NIAID/DMID Policy and Guidelines for Data and Safety Monitoring
7.3 NIH/NIAID/DMID DSMB Responsibilities
7.4 Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multi-center Clinical Trials
7.4 DMID Interventional Protocol template
7.5 DMID Standard Operating Procedure (Internal): *FDA Clinical Hold of DMID-sponsored INDs*
7.6 Council for International Organization of Medical Sciences (CIOMS)
7.7 *Management of Safety Information from Clinical Trials* – Report of CIOMS Working Group VI, Geneva 2005.

8.0 Inquiries:

Direct inquiries regarding this policy to;

Shy Shorer, MD
Director, Office of Clinical Research Affairs
NIH/NIAID/DMID
6610 Rockledge Dr.
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9.0 Availability:

This policy is located electronically,

NIAID public website
http://www3.niaid.nih.gov/LabsAndResources/resources/DMIDClinRsrch/safetyoversight.htm
DMID Intranet

10.0 Change Summary:

Version number	Date of Revision: DD/MMM/YYYY	Replaces	Effective Date: DD/MMM/YYYY	Description of Revision/Retirement
1.0	N/A	N/A	6-May-2009	N/A